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Andexanet alfa in Factor Xa Inhibitor-Associated Acute Major Bleeding

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- on behalf of the ANNEXA-4 investigators

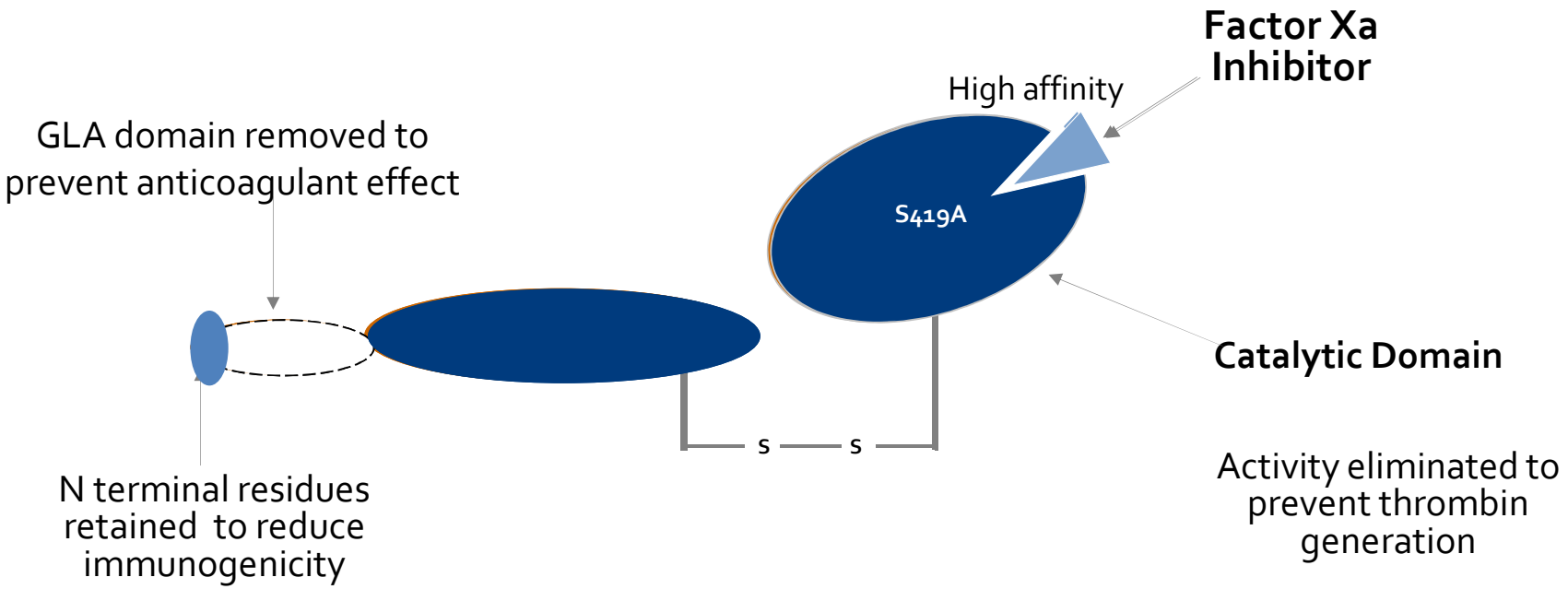
Background

- Factor Xa (FXa) inhibitors reduce thrombotic events, but can precipitate major bleeding
  - >100,000 bleeding hospitalizations per year in the US
  - Fatality rate of 15-20%
- Andexanet alfa was developed as a specific reversal agent for all direct and indirect FXa inhibitors
- It rapidly and safely reversed anti-FXa activity in healthy volunteers

Truven Health Analytics, 12 months ending December 31, 2016 for Commercial, Medicare, and Medicaid patients
Held C et al, Eur Heart J 2015; 36: 1264-72.
Piccini JP et al, Eur Heart J 2014; 35: 1873-80.

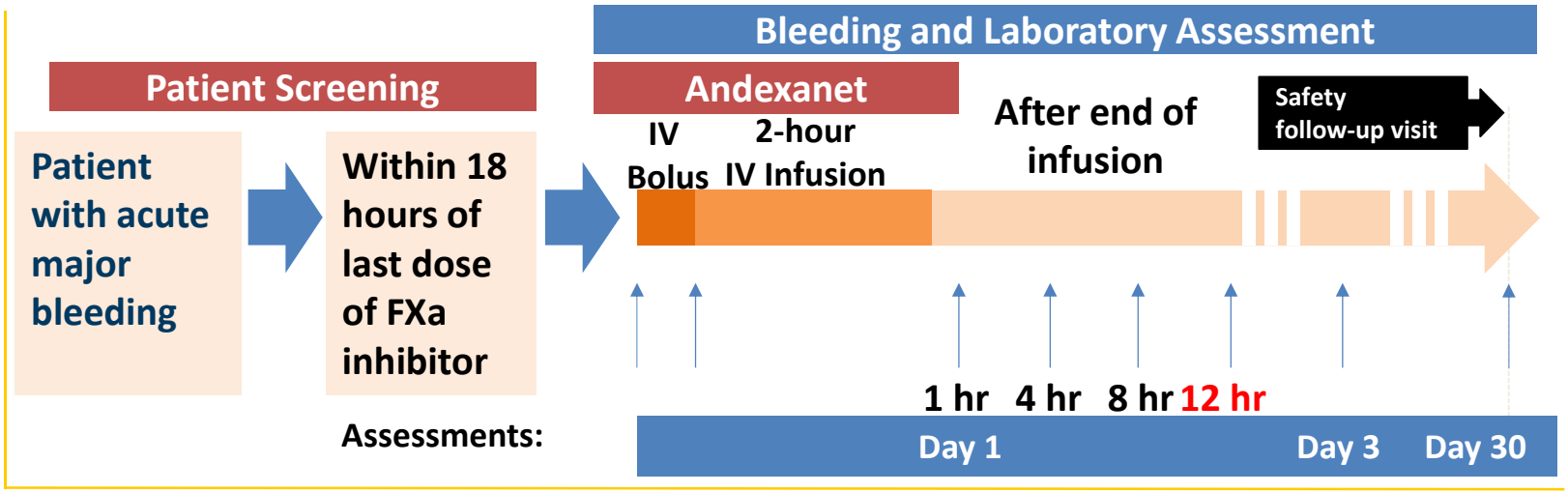
Andexanet alfa: Recombinant Modified Human Factor Xa

Factor Xa Decoy



Nature Medicine, Volume 19, April 2013

ANNEXA-4 Study Design



Efficacy Outcomes

- Change in anti-fXa activity
- Clinical hemostatic efficacy through 12 hours

Safety Measurements

- Thrombotic events
- Antibodies to FX, FXa, andexanet
- 30-day mortality

Key Eligibility Criteria

Inclusion Criteria

- Age > 18
- Acute major bleeding (any one)
  - Life-threatening, with evidence of hemodynamic compromise
  - Hgb decrease ≥ 2 g/dL
  - Critical area (e.g., ICH)
- Apixaban, edoxaban, enoxaparin, rivaroxaban
- Last dose of FXai within 18 hours

Exclusion Criteria

- Recent thrombotic event
- GCS < 7 or ICH volume > 60 cc
- Recent blood product use
- Expected mortality < 1 mo
- Planned surgery

ANNEXA-4 Dose Selection

Acute major bleeding ≤ 18 hours of last dose of apixaban, edoxaban, rivaroxaban, or enoxaparin

Andexanet IV bolus and 2 hour infusion

Pts on apixaban or >7 h from last rivaroxaban dose	Pts on enoxaparin, edoxaban or ≤7 h from last rivaroxaban dose
Bolus 400 mg + Infusion 480 mg @ 4 mg/min	**Bolus 800 mg + Infusion 960 mg @ 8 mg/min**

ANNEXA-4: Design and Analysis Plan

- **Analysis Populations**
  - **Safety** population includes all patients receiving andexanet
  - **Efficacy** population excludes patients with baseline anti-fXa activity <75 ng/ml (< 0.25 IU/ml for enoxaparin)
- **Interim analysis**
  - Includes all patients as of October 20, 2017
  - ANNEXA-4 study is ongoing

Assessment of Clinical Hemostatic Efficacy

- All cases assessed by independent committee
- Independent Core Lab interpreted brain CT and MRI
- Cases rated as excellent/good vs. poor/none based on specific criteria
- This methodology initially developed for assessment of 4F-PCC in warfarin bleeding, where efficacy reported was 72%*

**Sarode et al, Circulation 2013; 128, 1234-43*

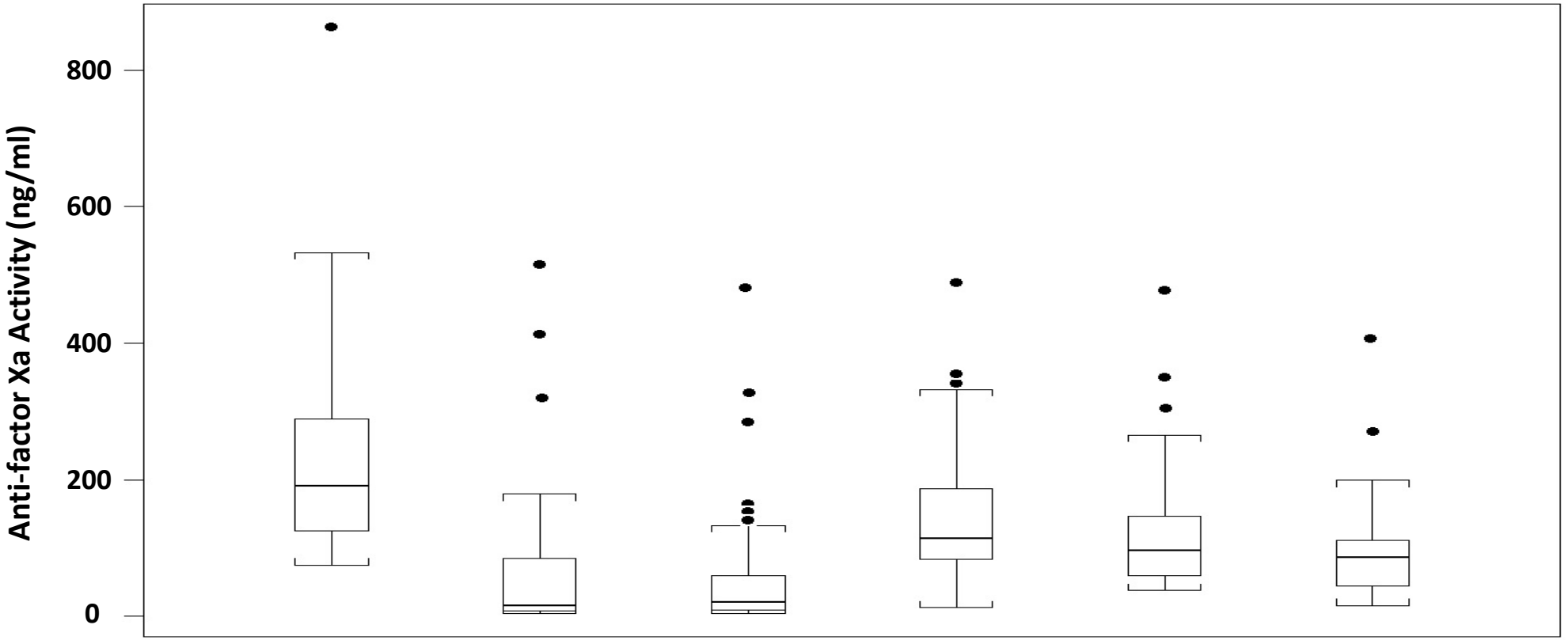
Baseline Characteristics

	Safety Population N=227	Efficacy Population N=137
Age (yr), mean ± SD	77(±11)	77 (±12)
Male	117 (52%)	70 (51%)
Time from presentation until Andexanet (hrs)	4.7 ± 2.8	5.0 ± 3.1
Estimated creatinine clearance < 30 mL/min,	21 (9%)	13 (10%)
Indication for anticoagulation		
Atrial fibrillation	178 (78%)	104 (76%)
Venous Thromboembolic Disease	52 (23%)	38 (28%)
Atrial fibrillation and VTE	8 (4%)	6 (4%)
Medical History		
Myocardial infarction	32 (14%)	15 (11%)
Stroke	47 (21%)	32 (23%)
Heart Failure	52 (23%)	36 (26%)
Diabetes mellitus	67 (30%)	42 (31%)

Site of Initial Bleeding

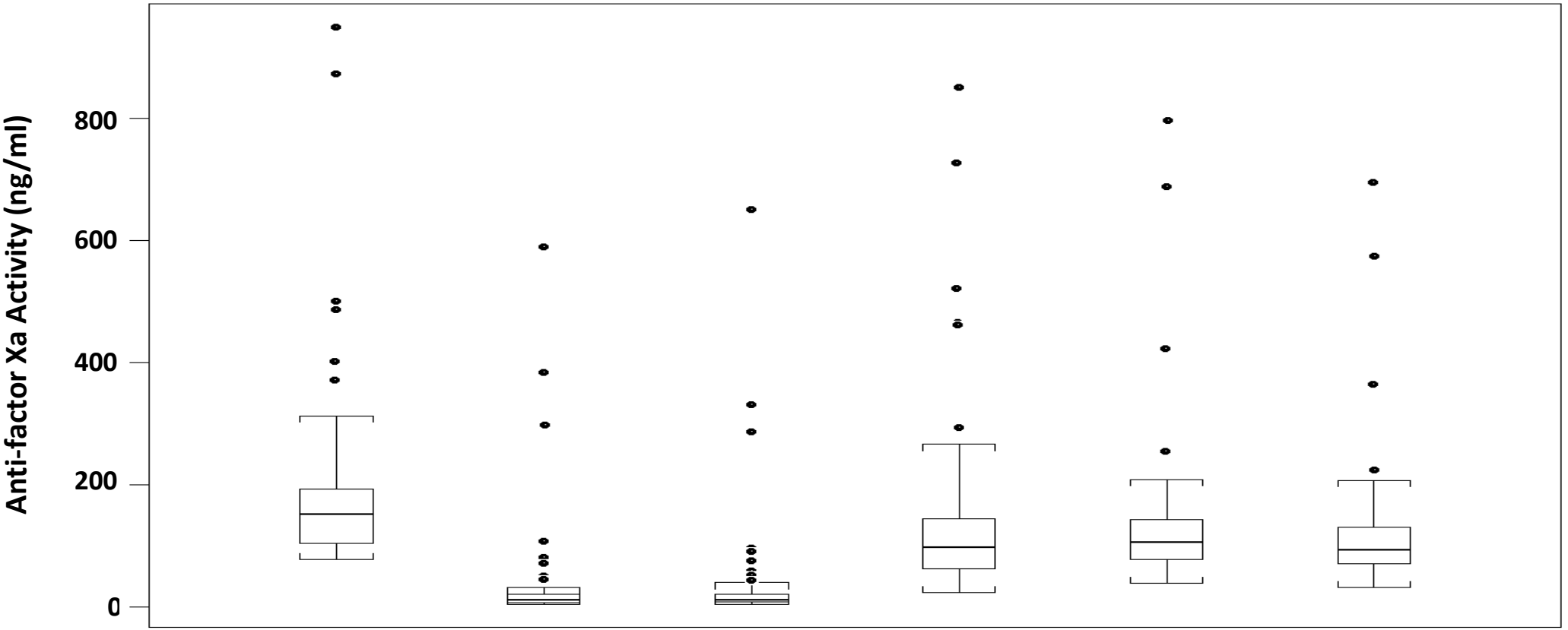
	Safety Population N=227	Efficacy Population N=137
Intracranial Bleeding	**139 (61%)**	**78 (57%)**
Glasgow Coma Scale, mean ± SD	13.9 ± 1.63	13.9 ± 1.70
Intracerebral site	74 (52%)	44 (54%)
Sub-dural site	45 (32%)	24 (30%)
Subarachnoid site	23 (16%)	13 (16%)
Gastrointestinal Bleeding	**62 (27%)**	**43 (31%)**
Other Bleeding site	**26 (12%)**	**16 (12%)**

Anti-factor Xa Activity: Rivaroxaban n= 75



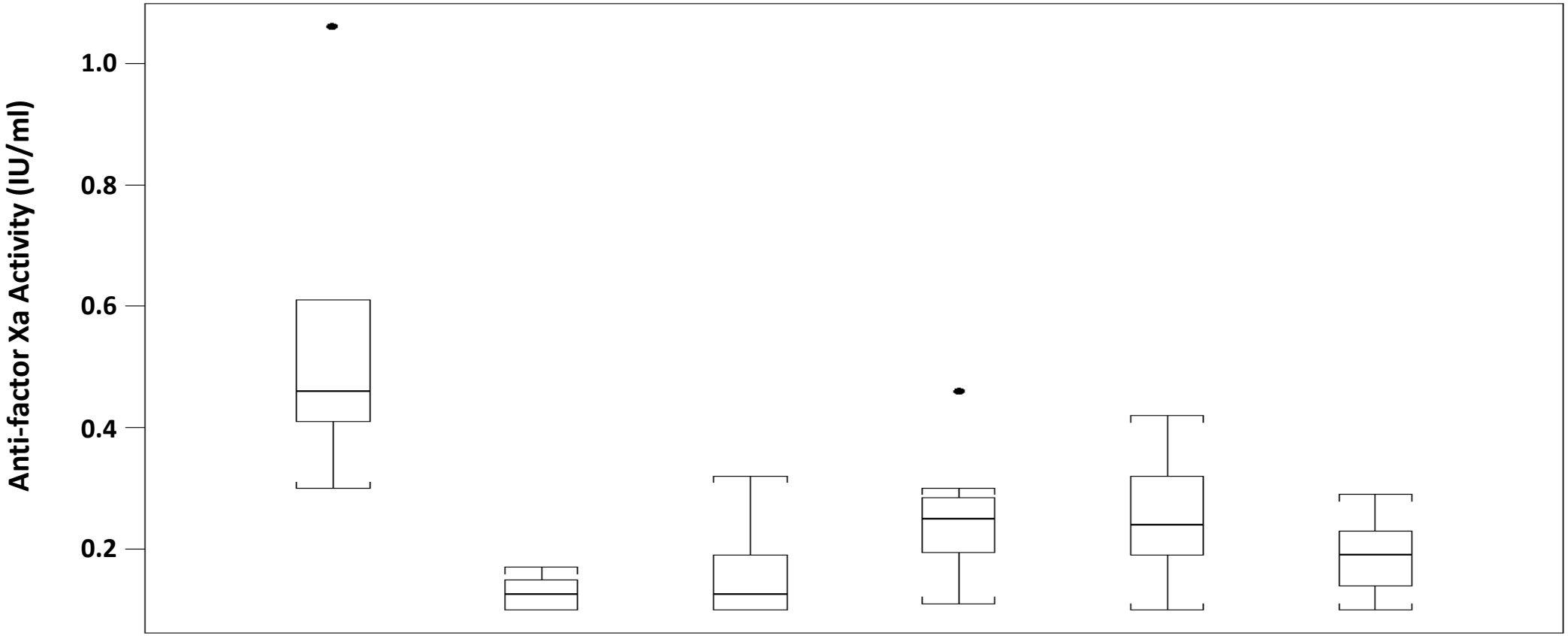
	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	169.75	11.30	14.40	96.80	82.60	72.20
Percent Change		-88%	-87%	-42%	-49%	-60%
(95% CI)		(-92 to -82)	(-89 to -82)	(-46 to -33)	(-53 to -45)	(-65 to -53)

Anti-factor Xa Activity: Apixaban n= 105



	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	132.60	9.45	10.10	79.65	90.05	80.90
Percent change		-91%	-91%	-36%	-30%	-35%
(95% CI)		(-92 to -90)	(-92 to -90)	(-41 to -29)	(-36 to -25)	(-41 to -32)

Anti-factor Xa Activity: Enoxaparin n= 16

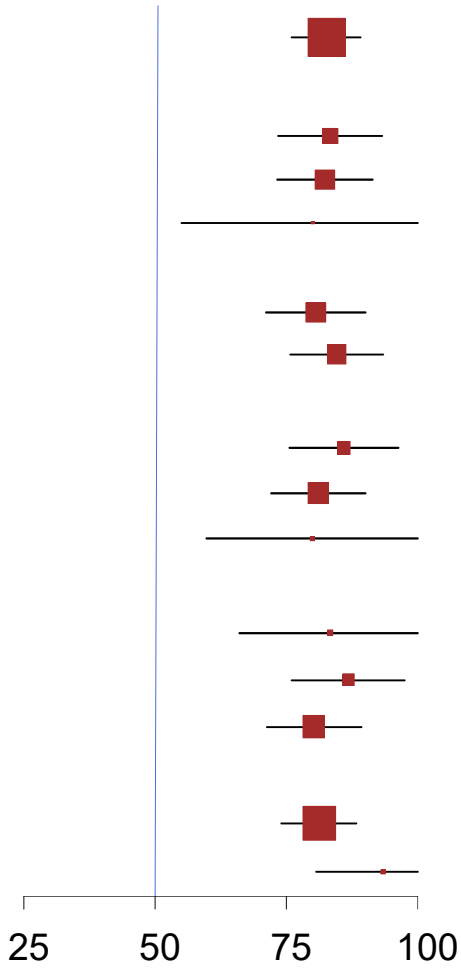


	Baseline	End of Bolus	End of Infusion	4 Hr	8 Hr	12 Hr
Median	0.44	0.11	0.11	0.23	0.21	0.18
Percent Change		-75%	-73%	-44%	-44%	-52%
(95% CI)		(-83 to -66)	(-79 to -29)	(-61 to -25)	(-60to -27)	(-67to -29)

Effective Hemostasis at 12 hours Post Andexanet

Number of Major Bleeds Adjudicated	Number of Patients who Achieved Excellent or Good Hemostasis	Percent of Patients who Achieved Excellent or Good Hemostasis	95% Confidence Interval
132	109	83%	76% - 89%

Clinical Hemostatic Efficacy



Subgroup	No. of Patients	Excellent or Good (95% CI)
Total Efficacy Patients	132	83 (76- 89)
Drug		
Rivaroxaban	54	83 (73- 93)
Apixaban	68	82 (73- 91)
Enoxaparin	10	80 (55-100)
Sex		
Male	67	81 (71- 90)
Female	65	85 (76- 93)
Site of bleeding		
Gastrointestinal	43	86 (76- 96)
Intracranial	74	81 (72- 90)
Other	15	80 (60-100)
Age		
<65 yr	18	83 (66-100)
65-75 yr	38	87 (76- 98)
>75 yr	76	80 (71- 89)
Andexanet dose		
Low	117	81 (74- 88)
High	15	93 (81-100)

Safety Assessment

- Thrombotic events occurred within 3 days of andexanet in 6 (2.6%) patients and by 30 days in 24 (11%)
- Anticoagulation re-started in 129 patients (57%) by 30 days
- Therapeutic anticoagulation was re-started in only 9 patients before a thrombotic event occurred
- 27 deaths occurred by 30 days (12%), of which 11 were cardiovascular

Recent Regulatory Trials of Approved Reversal Agents

Pivotal Study	Reversal agent Anticoagulant	Number		Hemostatic Efficacy (95% CI)		Thrombotic Event Rate (95% CI)	
		Total	% ICH	Total	ICH	Total	ICH
ANNEXA-4 *	Andexanet FXa Inhibitors	227	61	83% (76-89)	81% (72-90)	11% (7-16)	12% (7-19)
REVERSE-AD	Idarucizumab Dabigatran	301	33	68% [a]	NR [b]	5% (3-8)	6% (2-13)
Sarode 2013	4F-PCC Warfarin	98	12	72% (64-81)	42% (15-72)	8% (3-15)	NR
Sarode 2013	Plasma Warfarin	104	12	65% (56-75)	58% (28-85)	6% (3-13)	NR

4F-PCC = Four factor prothrombin complex concentrate; CI = Confidence interval; ICH = Intracranial hemorrhage; NR = Not reported
a 68% had investigator-determined, non-adjudicated time to hemostasis within 24 hours
b Time to hemostasis not calculated in ICH patients

Conclusions

- Andexanet rapidly reverses anti-fXa activity
- Effective hemostasis achieved in 83% of patients
- Thrombotic events/mortality rates consistent with the high risk profile of the patients
- Andexanet reversal of fXa inhibitor-bleeding has similar efficacy and safety as reported with other approved reversal agents